DRY POWDER PHARMACEUTICAL SUSPENSION COMPOSITIONS OF CEFUROXIME AXETIL

Field of the Invention

The present invention relates to dry powder pharmaceutical suspension compositions of cefuroxime axetil suitable for use as a liquid suspension wherein the composition has better bioavailability and is free of food effect. The present invention also relates to processes for the preparation of such compositions.

Background of the Invention

Cefuroxime axetil is a semi synthetic broad spectrum cephalosporin antibiotic for oral administration. Chemically, it is (RS)-1-hydroxyethyl (6R,7R)-7-[2-(2-furyl)glyoxylamido]-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate, 7^2-(Z)-(O-methyl-oxime),1 -acetate 3-carbamate. After oral administration, cefuroxime axetil is absorbed from the gastrointestinal tract and rapidly hydrolyzed to cefuroxime by nonspecific estrases present in the intestinal mucosa and blood. Commercially, cefuroxime axetil is available as tablets and oral suspension under the brand name Ceftin® marketed by GlaxoSmithKline, as well as being available from many other companies. The oral suspension is available in dry powder form which, when constituted with water provides 125mg or 250mg of cefuroxime per 5mL of suspension. Ceftin® oral suspension is an alternative for dosing pediatric patients who cannot swallow tablets. GlaxoSmithKline's labeling for Ceftin® powder for oral suspension states that the drug product contains the inactive ingredients acesulfame potassium, aspartame, povidone K30, stearic acid, sucrose, tutti-frutti flavoring, and xanthan gum.

As per the Physician's Desk Reference (PDR) and GlaxoSmithKline's labeling, Ceftin® for oral suspension is not bioequivalent to Ceftin® tablets on a mg/mg basis. In a study conducted by GlaxoSmithKline comparing the bioavailability of cefuroxime axetil for oral suspension and tablet in adults, the AUC of suspension was found to be 91% of that of the tablet, and the peak plasma concentration was found to be 71% of that of the tablet. Consequently, it is not recommending in the labeling that GlaxoSmithKline's oral tablet be substituted for their oral suspension dosage form. Orally dosing a patient with a cefuroxime axetil suspension with improved bioavailability of cefuroxime would be convenient and advantageous for elderly patients who have difficulty in swallowing and also for those medical conditions in which the patient is not able to swallow a tablet.

It has also been suggested that Ceftin oral suspension should be taken with food. In a study comparing the effect of food on the bioavailability of cefuroxime axetil, it was found that Ceftin® oral suspension showed a delay in the time of the peak plasma concentration (T_{max}) under fed conditions relative to that in fasting conditions. This is undesirable for effective therapy because the plasma levels necessary to show therapeutic effect are delayed and a quick onset of action may not be achieved.

U.S. Patent No. 4,865,851 describes the preparation of Ceftin® oral suspension that has cefuroxime axetil in particulate form, the particles being provided with integral coatings of a lipid or a mixture of lipids such as stearic acid and/or palmitic acid. The coated particles are prepared by atomizing a dispersion of particulate cefuroxime in the molten lipid and cooling the coated particles. The process is time consuming and requires complicated machinery to perform coating operations with strict control on process parameters such as temperature and pressure. Also, without being limited to any theory, the lipid coating may retard the dissolution of cefuroxime axetil and delay its absorption.

Summary of the Invention

In one general aspect there is provided a dry powder pharmaceutical suspension composition suitable for use as a liquid suspension. The composition includes granules that include cefuroxime axetil, at least one lubricant, and at least one glidant.

Embodiments of the composition may include one or more of the following features. For example, the composition may exhibit better bioavailability as compared to Ceftin® oral suspension. The composition may be free of food effects. The cefuroxime axetil may be up to about 99.89% by weight of the granules.

The lubricant may be one or more of stearic acid, calcium stearate, sodium stearyl fumarate and combinations thereof. The lubricant may be from about 0.01% to about 10% by weight of the granules. The glidant may be one or more of colloidal silicon dioxide and talc. The glidant may be about 0.1% to about 5% by weight of the granules.

The composition may further include one or more of suspending agents/viscosity enhancers, buffering agents, fillers, wetting agents, preservatives, flavouring agents, and sweeteners. The suspending agent/viscosity enhancer may be one or more of cellulosic derivatives, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methyl cellulose, sodium carboxymethylcellulose, gums, xanthan gum, guar gum; polysaccharides, starch,

pregelatinised starch, alginates, sodium alginate; acrylic acid copolymers, carbopols, polyvinylpyrrolidone, and combinations thereof.

The buffering agent may be one or more of monosodium citrate, sodium citrate, citric acid, and combinations thereof. The filler may be one or more of sucrose, starch, lactose, microcrystalline cellulose, and combinations thereof. The wetting agent may be one or more of sodium lauryl sulphate, polysorbates, tween 40, tween 60, tween 80, poloxamer, and combinations thereof. The preservative may be one or more of methyl paraben, propyl paraben, sodium benzoate, and combinations thereof. The flavouring agents/sweeteners may be one or more of grenadine flavour, tutti frutti flavour, peppermint flavour, aspartame, saccharine sodium, sucrose, sorbitol, sodium cyclamate and combinations thereof.

The granules may include up to approximately 315 mg of cefuroxime axetil per 5 ml of suspension, up to approximately 6 mg of colloidal silicon dioxide per 5 ml of suspension, and up to approximately 6 mg of stearic acid per 5 ml of suspension. The composition may include approximately 3979 mg of sucrose per 5 ml of suspension, approximately 20 mg of aspartame per 5 ml of suspension, approximately 84 mg of silicon dioxide per 5 ml of suspension, approximately 10 mg of monosodium citrate per 5 ml of suspension, approximately 19 mg of flavour per 5 ml of suspension, and approximately 10 mg of sodium chloride per 5 ml of suspension.

In another general aspect there is provided a process of forming a dry powder pharmaceutical suspension composition suitable for use as a liquid suspension. The process includes forming granules by granulating a mixture of cefuroxime axetil, at least one lubricant, and at least one glidant by compaction/slugging.

Embodiments of the process may include one or more of the following features. For example, the process may further include sizing the granules. The granules may be prepared by compaction. The cefuroxime axetil may e up to about 99.89% by weight of the granules.

The lubricant may be one or more of stearic acid, calcium stearate, sodium stearyl fumarate, and combinations thereof. The lubricant may be from about 0.01% to about 10% by weight of the granules. The glidant may be one or more of colloidal silicon dioxide and talc. The glidant may be from about 0.1% to about 5% by weight of the granules.

The process may further include mixing one or more additional pharmaceutical excipients with the granules. The additional pharmaceutical excipients may be one or more of suspending agents/viscosity enhancers, buffering agents, fillers, wetting agents, preservatives, flavouring agents and sweeteners.

In another general aspect there is provided a method of dosing for infections treated with cefuroxime axetil. The method includes administering a dry powder pharmaceutical suspension composition of cefuroxime axetil dissolved or suspended in an ingestible liquid. The composition includes granules that include cefuroxime axetil, at least one lubricant, and at least one glidant.

Embodiments of the method may include any one or more of the features described above.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

Detailed Description of the Invention

In view of the above description in background, it would be advantageous to develop an oral suspension of cefuroxime axetil that not only provides improved bioavailability in comparison to Ceftin® oral suspension but is also free of food effects. Further, it would be advantageous to provide a process for the preparation of such a suspension that is convenient, economical, and requires simple machinery.

We have now discovered that dry powder pharmaceutical suspension compositions of cefuroxime axetil can be prepared by granulating a mixture of cefuroxime axetil, lubricant, and glidant. The granules when constituted as a liquid suspension not only provide better bioavailability as compared to the marketed Ceftin® oral suspension but is also free of food effects. These granules may be administered as a suspension or taken with a glass of water. The suspension of granules is particularly convenient for elderly patients.

The term "dry powder" as used herein includes any composition which is dry and flowable such as, for example, granules, flakes, spheroids and other forms which can be readily prepared and when added to an ingestible liquid and mixed, give the desired liquid suspension.

Cefuroxime axetil as used herein may be in crystalline form or in amorphous form, for example, as described in GB 2127401 and may be present in granules that include a mixture of cefuroxime axetil, one or more lubricants, and one or more glidants and, optionally, other pharmaceutical excipients. The size of the granules is preferably less than 250μm. The cefuroxime axetil may be present at up to about 99.89% by weight of the granules.

The lubricants can be selected from one or more of stearic acid, calcium stearate, sodium stearyl fumarate, and combinations thereof. The lubricant in the granules can be from about 0.01% to about 10% by weight of the granules.

The glidant can be selected from one or both of colloidal silicon dioxide and talc. The concentration of glidant can be from about 0.1% to about 5% by weight of the granules.

The oral suspension may comprise other pharmaceutical excipients, such as suspending agents/viscosity enhancers, buffering agents, fillers, wetting agents, preservatives, flavouring agents and sweeteners.

The suspending agents/viscosity enhancers may be selected from one or more of cellulosic derivatives such as hydroxypropyl cellulose, hydroxypropyl methylcellulose, methyl cellulose, and sodium carboxymethylcellulose; gums such as xanthan gum and guar gum; polysaccharides such as starch and pregelatinised starch; alginates such as sodium alginate; acrylic acid copolymers such as carbopols; polyvinylpyrrolidone; and combinations thereof.

The buffering agent may be selected from monosodium citrate, sodium citrate, citric acid and combinations thereof.

The fillers may be selected from sucrose, starch, lactose, microcrystalline cellulose and combinations thereof.

The wetting agent may be selected from sodium lauryl sulphate, polysorbates such as tween 40, tween 60, tween 80, poloxamer and combinations thereof.

The preservatives may be selected from methyl paraben, propyl paraben, sodium benzoate or a combination thereof.

The flavouring agents may be selected from, for example, grenadine flavour, tutti frutti flavour and peppermint flavour while the sweeteners may be selected from, for example, aspartame, saccharine sodium, sucrose, sorbitol and sodium cyclamate and combinations thereof.

The pharmaceutical composition as described herein may be formed as a suspension for administration, as a dry product for constitution with an ingestible liquid such as water before use for administration as a suspension, or for direct administration and then washed down with water or other ingestible liquid. The dry powder for suspension can be packed in suitable containers to provide multidose or a single unit dose liquid suspension.

The dry powder pharmaceutical suspension may be prepared by the general procedure that includes dry blending cefuroxime axetil, at least one lubricant, and at least one glidant; granulating by compaction/slugging; sizing; and optionally mixing with other pharmaceutical excipients. These are then filled into a bottle or a suitable container in an amount suited to a dosage regimen. A suitable ingestible liquid, particularly water, is added in an amount sufficient to provide cefuroxime axetil in desired dosage strength. Typically, the dry powder after constitution with an ingestible liquid is set to provide a liquid suspension containing 125mg or 250mg of cefuroxime axetil per 5mL of liquid suspension.

The dry powder pharmaceutical suspension composition is stable on storage and when constituted with an ingestible liquid for administration, the corresponding liquid suspension is stable for the duration in which the therapy is required.

As per one of the embodiments of the process, the dry powder for cefuroxime oral suspension may be prepared by the following steps:

1. Cefuroxime axetil, stearic acid, colloidal silicon dioxide are blended in a suitable mixer.
2. The blend of step 1 is then granulated by compaction or slugging.
3. The granules of step 2 are sized and mixed with one or more other optional excipients.
4. The final blend is packed in HDPE bottles.

The following example is provided to illustrate one embodiment of the invention but is not intended to be limiting.

Example 1

Ingredients	Quantity/5ml
Cefuroxime axetil granules	
Cefuroxime axetil (eq. to 250mg Cefuroxime)	315.78
Colloidal silicon dioxide	6.0
Stearic acid	6.0
Sucrose	3979.21
Aspartame	20.00
Silicon dioxide	84.00
Monosodium citrate	10.00
Flavour	19.00
Sodium chloride	10.00
Total weight	**4450.00**

Method:

Cefuroxime axetil, colloidal silicon dioxide and stearic acid were blended in a suitable mixer. The blend was compacted to form granules which were sized and screened through a BSS # 60 Sieve (250 microns). Sucrose, aspartame, silicon dioxide, monosodium citrate, flavour and sodium chloride were sifted and blended with the above cefuroxime axetil granules. The final blend was packed in high density polyethylene (HDPE) bottles.

Bioavailability studies:

The oral Cefuroxime axetil suspension of Example 1 and Ceftin® oral suspension (GlaxoSmithKline) were evaluated for pharmacokinetic parameters in 24 healthy human adult volunteers under fasting and fed conditions in separate comparative, randomized, single-dose (eq. to 500mg of cefuroxime), 2-way crossover bioavailability studies. Table 1 gives the details of the observed pharmacokinetic parameters in the study conducted under fasting conditions. Table 2 gives the details of pharmacokinetic parameters observed under fed conditions.

Table 1 Pharmacokinetic Parameters (mean values) of Oral Suspension of Example 1 and Ceftin® Oral Suspension in human volunteers following administration of a 500mg dose under fasting conditions.

	AUC_{0-t} (mcg.h/mL)	$AUC_{0-\infty}$ (mcg.h/mL)	C_{max} (mcg/mL)	T_{max} (hours)
Example 1 (Test)	22.394	22.764	6.421	1.966
Ceftin® Oral Suspension (Reference)	20.618	21.188	5.475	2.356

The oral suspension of Example 1 (Test) under fasting conditions has shown higher values for both AUC_{0-t} as well as $AUC_{0-\infty}$ as compared to Ceftin® oral suspension. The AUC_{0-t} showed an increase of about 8.61% and AUC_{0-} showed an increase of about 7.43%. The C_{max} showed an increase of about 17.27%. The time of peak plasma concentration (T_{max}) was achieved about 0.39 hours earlier.

Table 2 Pharmacokinetic Parameters (mean values) of Oral Suspension of Example 1 and Ceftin® oral suspension in human volunteers following administration of a 500mg dose under fed conditions.

	AUC_{0-t} (mcg.h/mL)	$AUC_{0-\infty}$ (mcg.h/mL)	C_{max} (mcg/mL)	T_{max} (hours)
Example 1 (Test)	30.830	31.389	7.053	2.462
Ceftin® Oral Suspension (Reference)	24.622	27.163	4.737	4.667

The oral suspension of Example 1 (Test) under fed conditions has shown higher values for both AUC_{0-t} as well as $AUC_{0-\infty}$ as compared to Ceftin® oral suspension. The AUC_{0-t} showed an increase of about 25.21% and $AUC_{0-\infty}$ showed an increase of about 15.55%. The C_{max} showed an increase of about 48.89%. The time of peak plasma concentration (T_{max}) was achieved about 2.2 hours earlier.

Table 3 Pharmacokinetic Parameters (mean values) of Oral Suspension of Example 1 and Ceftin® Tablet in human volunteers following administration of a 500mg dose under fed conditions.

	$AUC_{0-\infty}$ (mcg.h/mL)	C_{max} (mcg/mL)	T_{max} (hours)
Example 1 (Test)	31.389	7.053	2.462
Ceftin®Tablet (Reference)	27.4	7.0	3.0

The oral suspension of Example 1 provides values of pharmacokinetic parameters for cefuroxime in human volunteers comparable to those given by Ceftin® tablets as shown in Table 3.

These data suggest the feasibility of substituting Ceftin® oral tablets with the oral suspension of example 1 in cases including pediatric patients where tablets are not a convenient mode of administration.

While several particular forms of the inventions have been described, it will be apparent that various modifications and combinations of the inventions detailed in the text can be made without departing from the spirit and scope of the inventions. Accordingly, it is not intended that the inventions be limited, except as by the appended claims.